PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 519/00, 501/46
A61K 31/545

A1

(11) International Publication Number: WO 92/22556

(43) International Publication Date: 23 December 1992 (23.12.92)

(21) International Application Number: PCT/KR92/00016

(22) International Filing Date: 18 May 1992 (18.05.92)

(30) Priority data:
1991-9930 15 June 1991 (15.06.91) KR
1992-2067 12 February 1992 (12.02.92) KR

(71) Applicant: CHEIL FOODS & CHEMICALS, INC. [KR/KR]; 150, Taepyungro 2-ga, Chung-ku, Seoul 100-102 (KR).

(72) Inventors: KIM, Choong, Sup ; 264-465, Imoon 2-dong, Tongdaemoon-ku, Seoul 130-082 (KR). AN, Seung, Ho ; 151-7, Karak-dong, Songpa-ku, Seoul 138-160 (KR). CHO, Sung, Ki ; 172, Bangbae-dong, Sucho-ku, Seoul 137-060 (KR). AHN, Yang, Soo ; 912-408 Jukong Apt., Myungil 2-dong, Kangdong-ku, Seoul 134-072 (KR). CHOI, Kyoung, Eob ; 102-204 Family Apt., Moonjeong-dong, Songpa-ku, Seoul 138-200 (KR). KIM, Je, Hak ; 201-1301 Woomanjukong Apt., Wooman-dong, Changan-ku, Suwon-shi, Kyonggi-do 440-190 (KR). YUN, Rok, Lim ; 105-310 Shinbanpo Apt., In.ye-dong, Kwonsun-ku, Suwon-shi, Kyonggi-do 441-070 (KR). PARK, Sung, Yong ; 669-1, Eungam 2-dong, Eunpyung-ku, Seoul 122-012 (KR). YOON, Yeo, Hong ; 609-10, Kongneung-dong, Nowon-ku, Seoul 139-240 (KR). LYU, Chun, Seon ; 614-232, Bangwha 2-dong, Kangsu-ku, Seoul 157-222 (KR). LEE, Koun, Ho ; 281-148, Galhyun-dong, Eunpyung-ku, Seoul 122-050 (KR).

(74) Agent: LEE, Kuiy, Dong; 114-31, Uni-dong, Chongro-ku, Seoul 110-350 (KR).

(81) Designated States: AT, AU, BE (European patent), BG, CA, CH, DE, ES, FI, FR (European patent), GB, HU, IT (European patent), JP, NL, RU, SE.

Published
With international search report.

(54) Title: NOVEL 3-FUSED PYRIDINIUMMETHYL CEPHALOSPORINS

(57) Abstract

Novel semi-synthetic cephalosporin derivatives having a fused pyridiniummethyl at 3-position of the cephem nucleus, pharmaceutically acceptable salts, physiologically hydrolizable esters or solvates thereof are disclosed. Also disclosed is a process for preparing the cephalosporin derivatives which comprises introducing a fused pyridiniummethyl substituent at 3-position of 7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamino]-3-cephem-carboxylic acid derivatives. The compounds of the present invention show potent antibacterial activities and a broad spectrum against both gram-positive and gram-negative bacterial.

59

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	ML	Mali
AU	Australia	FR	France	MN	Mongolia
BB	Barbados	GA	Gabon	MR	Mauritania
BE	Belgium	GB	United Kingdom	MW	Malawi
BF	Burkina Faso	GN	Guinea	NL	Netherlands
BG	Bulgaria	GR	Greece	NO	Norway
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IE	Ireland	RO	Romania
CA	Canada	IT	Italy	RU	Russian Federation
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland			SN	Senegal
CI	Côte d'Ivoire	KR	Republic of Korea	SU	Soviet Union
CM	Cameroon	LI	Liechtenstein	TD	Chad
CS	Czechoslovakia	LK	Sri Lanka	TG	Togo
DE	Germany	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		
ES	Spain	MG	Madagascar		

NOVEL 3-FUSED PYRIDINIUMMETHYL CEPHALOSPORINS

TECHNICAL FIELD

The present invention relates to novel cephalosporin derivatives, a pharmaceutically acceptable salt, and physiologically hydrolyzable ester and solvate thereof. This invention also relates to a process for their preparation, a use thereof as an antibiotic, and a pharmaceutical composition containing the same derivatives as an active ingredient.

BACKGROUND ART

A number of cephalosporin compounds have been synthesized in which the cephem nucleus has a quarternary ammonium methyl at its 3-position and various acylamino groups at its 7-position. These compounds exhibit selective toxicity against bacteria only and present no substantial effects against animal cells. They have been widely used for the treatment of infectious diseases caused by bacteria as antibiotics having no substantial side effects. Thus, they are highly useful as drugs.

In recent years, an extensive investigation has been made to develop novel cephalosporin derivatives which have more potent antibacterial activities and a broad antibacterial spectrum, especially coupled with activities against cephalosporin resistant bacteria.

As a result, a number of cephalosporin derivatives have been developed which have a 2-(2-aminothiazol-4-yl)-2-substituted oxyiminoacetamido group as a side chain at 7-

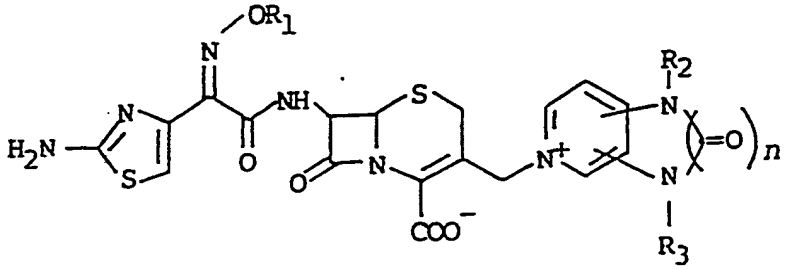
position and a fused pyridiniummethyl substituted at 3-position of the cephem nucleus. As prior art references which disclose such derivatives, U.S. Patent No. 4,152,432 to Heymes et al., U.S. Patent No. 4,098,888 to Ochiai et al., U.S. Patent No. 4,258,041 to O'Callaghan, U.S. Patent No. 4,748,172 to Katner, European Patent No. 0,138,552 to Katner, European Patent No. 0,164, 944 to Bradbury, and European Patent No. 0,300,664 to Jung may be mentioned.

The present invention has been accomplished as an advanced improvement as compared with such investigation.

Thus, the object of the invention is to provide novel cephalosporin derivatives having strong activities and a broad antibacterial spectrum against both gram-positive and gram-negative bacteria, as well as excellent stability against ß-lactamase.

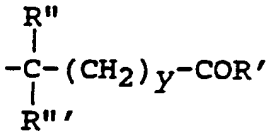
DISCLOSURE OF THE INVENTION

The present invention provides novel cephalosporin derivatives having the formula:



(I)

wherein R_1 is hydrogen, or a lower alkyl, C_3-C_4 alkenyl, C_3-C_4 alkynyl or cycloalkylalkyl group, a fluoro-substituted lower alkyl group represented by the formula: $-(CH_2)_xF$ in which x is an integer of 1 to 3, or a carboxy-substituted alkyl group represented by the formula:



wherein R′ is a hydroxy, amino or C_1-C_4 alkoxy group; R" and R"′, which may be the same or different, represent hydrogen or a C_1-C_3 alkyl group, or R" and R"′ together with the carbon atom to which they are attached may form a C_3-C_7 carbocyclic ring; and *y* is an integer of 0 to 3;

R_2 and R_3, which may be the same or different, represent hydrogen, or a lower alkyl, amino, carboxy-substituted lower alkyl, hydroxy-substituted lower alkyl or C_3-C_7 cycloalkyl group;

n is an integer of 1 or 2; and

the 2-oxo-heterocyclic moiety is fused with the pyridine ring to form a 2,3- or 3,4-fused ring substituent at 3-position of the cephem nucleus; or a pharmaceutically acceptable salt, physiologically hydrolyzable ester or solvate thereof.

The compounds of the present invention show strong activities against gram-positive bacteria such as *Streptococcus*, *Staphylococcus*, Methicillin resistant *Staphylococcus*, *Corynebacterium*, *Bacillus*, etc.; gram-negative bacteria such as *Escherichia*, *Enterobacter*, *Klebsiella*, *Serratia*, *Salmonella*, *Proteus*, *Providensia*, *Morganella*, *Pseudomonas*, etc.; and various drug resistant bacteria.

Particularly preferred specific compounds according to the invention are as set forth below:

7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacet-

amido]-3-[2,3(1H,4H)-dioxo-pyrazino[5,6-c]pyridinium-methyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-[2,3(1H,4H)-dioxo-pyrazino[5,6-c]pyridinium-methyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-aminothiazol-4-yl)-2-propynyloxyiminoacetamido]-3-[2,3(1H,4H)-dioxo-pyrazino[5,6-c]pyridinium-methyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-cyclopropylmethoxyiminoacetamido]-3-[2,3(1H,4H)-dioxo-pyrazino[5,6-c]-pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-[2,3(1H,4H)-dioxo-pyrazino[5,6-c]-pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-yl)oxyiminoacetamido]-3-[2,3(1H,4H)-dioxo-pyrazino-[5,6-c]-pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[1-methyl-2,3(4H)-dioxo-pyrazino[5,6-c]-pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[1-ethyl-2,3(4H)-dioxo-pyrazino[5,6-c]-pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[1-cyclopropyl-2,3(4H)-dioxo-pyrazino[5,6-c]-pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-yl)oxyiminoacetamido]-3-[1-methyl-2,3(4H)-dioxo-pyrazino[5,6-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-yl)oxyiminoacetamido]-3-[1-ethyl-2,3(4H)-dioxo-pyrazino[5,6-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-yl)oxyiminoacetamido]-3-[1-cyclopropyl-2,3(4H)-dioxo-pyrazino[5,6-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[4-methyl-2,3(1H)-dioxo-pyrazino[5,6-c]-pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(aminothiazol-4-yl)-2-fluoromethoxyiminoacetamido]-3-[2,3(1H,4H)-dioxo-pyrazino[5,6-c]-pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2(1H,3H)-oxo-imidazo[4,5-c]pyridinium-methyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[1-methyl-2(3H)-oxo-imidazo[4,5-c]pyridinium-methyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[1-amino-2(3H)-oxo-imidazo[4,5-c]pyridinium-methyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[1-(2-hydroxyethyl)-2(3H)-oxo-imidazo[4,5-c]-pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2(1H,3H)-oxo-imidazo[4,5-b]pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-fluoromethoxyiminoacetamido]-3-[2(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-fluoromethoxyiminoacetamido]-3-[1-methyl-2(3H)-oxo-imidazo[4,5-c]-pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-fluoromethoxyiminoacetamido]-3-[1-amino-2(3H)-oxo-imidazo[4,5-c]-pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-fluoromethoxyiminoacetamido]-3-[2(1H,3H)-oxo-imidazo[4,5-b]pyridiniummethyl]-3-cephem-4-carboxylate; and

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-[2(1H,3H)-oxo-imidazo[4,5-c]-pyridiniummethyl]-3-cephem-4-carboxylate.

The new cephalosporin compounds of the present invention may be in the form of either a *syn*- or *anti*-isomer, or a mixture thereof consisting of at least about 90 % of a *syn*-isomer and not more than 10 % of an *anti*-isomer.

Also, if R_1 is a carboxy-substituted alkyl group

represented by the formula: -C(R")(R"')COOH wherein R" and R"' are different from each other, then the carbon atom to which R" and R"' are linked may be an asymmetrical center, resulting in diastereoisomers. Therefore, the present invention also includes such diastereoisomers of the cephalosporin derivatives of the formula (I) above, and mixtures thereof.

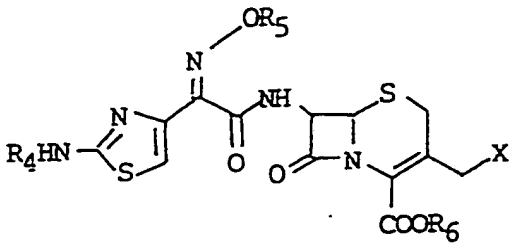
The compounds of the formula (I) may be converted to non-toxic salts thereof by conventional methods. Such non-toxic salts may be pharmaceutically acceptable salts of the compound of the formula (I). Included among the non-toxic salts are an inorganic salt, for example, a metal salt such as an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), ammonium salt, and so forth; an organic salt, for example, an organic amine salt (e.g., trimethylamine salt, triethylamine salt, pyridine salt, procaine salt, picoline salt, decyclohexylamine salt, N,N-dibenzylethylenediamine salt, N-methyl glucamine salt, diethanolamine salt, triethanolamine salt, tris(hydroxy-methylamino)methane salt, phenylethylbenzylamine salt, dibenzylethylenediamine salt, and so forth; an organic carboxylic or sulfonic acid salt (e.g., formate, acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.); an inorganic acid salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.); a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, lysine, etc.); and the like.

The physiologically hydrolyzable esters of the compounds of the formula (I) may include, for example, indanyl, phthalidyl, methoxymethyl, pivaloyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl or 5-methyl-2-oxo-1,3-dioxolan-4-yl esters, and other physiologically

hydrolyzable esters which have been widely used in penicillin and cephalosporin antibiotics chemistry.

The present invention further provides a process for preparing the novel cephalosporin derivatives of the formula (I) comprising the steps of:

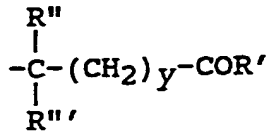
reacting a compound of the formula:



(II)

wherein R_4 is an amino protecting group;

R_5 is hydrogen, or a lower alkyl, C_3-C_4 alkenyl, C_3-C_4 alkynyl or cycloalkylalkyl group, a fluoro-substituted lower alkyl represented by the formula: $-(CH_2)_xF$, in which x is an integer of 1 to 3, or a carboxy-substituted alkyl group represented by the formula:

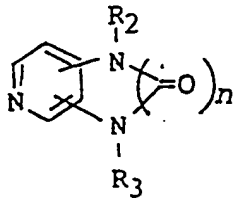


wherein R′ is a hydroxy, amino or C_1-C_4 alkoxy group; R" and R"′ may be the same or different and represent hydrogen or a C_1-C_3 alkyl group, or R" and R"′ together with the carbon atom to which they are attached may form a C_3-C_7 carbocyclic ring; and y is an integer of 0 to 3;

R_6 is a carboxyl protecting group; and

X is a leaving group;

with a compound of the formula:



(III)

wherein R_2, R_3 and n have the same meaning as defined above and the 2-oxo-heterocyclic moiety is fused with the pyridine ring to form a 2,3- or 3,4-fused ring; and then, if necessary, removing the amino protecting group and/or the carboxyl protecting group.

In the preparation of the objective compounds of the formula (I), the compound of the formula (II) is preferably used in an amount of from 1 to 2 equivalents based on 1 equivalent of the compound of the formula (III).

Now, the symbols and terms used in the specification will be explained.

The term "lower" as used herein above and elsewhere in this specification, for example, with reference to "lower alkyl," means those group having 1 to 6, preferably 1 to 4 carbon atoms.

The amino protecting group may include an acyl group; a substituted or unsubstituted aryl-lower alkyl group, for example, benzyl, diphenylmethyl, triphenylmethyl and 4-methoxybenzyl; a halo-lower alkyl group, for example, trichloromethyl and trichloroethyl; tetrahydropyranyl; a substituted phenylthio group; a substituted alkylidene group; a substituted aralkylidene group; and a substituted cyclolidene group. The acyl group as an amino protecting

group may include, for example, a C_1-C_6 alkanoyl group such as formyl and acetyl; a C_2-C_6 alkoxy carbonyl group, for example, methoxycarbonyl and ethoxycarbonyl; a lower alkane sulfonyl group, for example, methane sulfonyl and ethane sulfonyl; or an aryl-lower alkoxy carbonyl group such as benzyloxycarbonyl. One to three substituents such as a halogen atom, or a hydroxy, cyano or nitro group can further be substituted for the acyl group. In addition, the amino protecting group may include the reaction products formed by a reaction of an amino group with silane, boron, or phosphorous compounds.

The carboxyl protecting group such as R_6 may include, for example, a lower alkyl group such as methyl and t-butyl; a lower alkenyl group such as vinyl and allyl; a lower alkoxy-lower alkyl group such as methoxymethyl; a lower alkylthio-lower alkyl group such as methylthiomethyl; a halo-lower alkyl group such as 2,2,2-trichloroethyl; a substituted or unsubstituted aralkyl group such as benzyl and p-nitrobenzyl; or a silyl group.

The amino or carboxyl protecting groups mentioned above may be readily removed under mild conditions by using a known method(See: *Protecting Groups in Organic Synthesis*, 3rd Ed.).

The leaving group, X, may include; for example, a halogen atom such as fluorine, chlorine, and iodine; a lower alkanoyloxy group such as acetoxy; a lower alkanesulfonyloxy group such as methanesulfonyloxy; an arenesulfonyloxy group such as p-toluenesulfonyloxy; an alkoxy carbonyloxy group; and the like.

BEST MODE FOR CARRYING OUT THE INVENTION

The displacement reaction of the compound of the formula (II) with the compound of the formula (III) is well performed when X is an acetoxy group or an iodine atom.

In an embodiment, a compound of the formula (II) in which X is an acetoxy group is first silylated with a silylating agent to protect the carboxy group at 4-position and the amino group of the substituent at 7-position. As the silylating agent, mono- or bis-trimethylsilylacetamide, N-methyl-N-(trimethylsilyl)acetamide, N,O-bis(trimethylsilyl)trifluoroacetamide, N-methyl-N-(trimethylsilyl)trifluoroacetamide (MSTFA) and hexamethyldisilazane (HMDS) may be used.

The silylated compound of the formula (II) is then reacted with trimethylsilyliodide (TMSI) at ambient temperature to form a compound of the formula (II) in which X is iodine. This reaction can be carried out in accordance with a known method, for example, as taught by U.S. Patent No. 4,266,049 to Bonjouklian.

Separately, the fused pyridine of the formula (III) is silylated at room temperature in an aprotic organic solvent using the same silylating agent as mentioned above.

The resulting silylated 3-iodomethyl cephalosporin of the formula (II) is then reacted with the silylated fused pyridine of the formula (III) to give a silylated compound of the formula (I). Hydrolysis of the silyl groups provides a compound of the formula (I) according to the present invention.

The reaction for introducing the substituent of the

formula (III) at 3-position of the compound of the formula (II) to prepare the compound of the formula (I) is carried out in the presence of an organic solvent such as an anhydrous aprotic solvent. As an appropriate organic solvent, there may be mentioned a nitrile solvent such as acetonitrile and propionitrile; an alkyl halide solvent such as chloroform, carbon tetrachloride and dichloromethane; an ether solvent such as tetrahydrofuran and dioxane; an amide solvent such as N,N-dimethyl formamide; an ester solvent such as ethylacetate and methylacetate; a ketone solvent such as acetone, methyl ethyl ketone and methyl isobutyl ketone; a sulfoxide solvent such as dimethylsulfoxide; and an aromatic carbohydrogen solvent such as benzene and toluene. This reaction may be carried out at 0 ^{o}C to 25 ^{o}C.

In an alternative embodiment, the compounds of the formula (I) according to the invention are prepared directly from a 3-acetoxymethyl compound, for example, a compound of the formula (II) in which X is an acetoxy and R_4 is H.

This reaction is carried out in a conventional manner, for instance, in an aqueous medium, for example in an organic solvent in admixture with water. Addition of a small amount of an alkali iodide such as potassium iodide can enhance the rate of the reaction. This reaction is carried out at a temperature between about 35 ^{o}C and about 70 ^{o}C. Useful water miscible organic solvents include acetone, acetonitrile, tetrahydrofuran, and dimethylacetamide.

However, it is preferred to use the former method, i.e., reacting a compound of the formula (II) in which X is iodine with a compound of the formula (III) in view of the

reactivity and yields.

The amino or acid protecting groups can be readily removed by a conventional deprotection method well known in cephalosporin antibiotics chemistry. For example, acid- or base-hydrolysis or reduction are generally applicable. For example, when the protecting group is an amido group, such compound is subjected to imino-halogenation and imino-etherification, followed by hydrolysis. Acid hydrolysis is preferably applicable to the removal of the groups such as tri(di)-phenylmethyl or alkoxycarbonyl. As a preferred acid for this purpose, there may be mentioned organic acids such as formic acid, trifluoroacetic acid and p-toluene-acetic acid; or an inorganic acid such as hydrochloric acid and the like.

During and after the preparation, a stabilizing agent can be used to stabilize reaction products and their intermediates. As a stabilizing agent, one or more salts selected from the group consisting of sodium iodide, potassium iodide, sodium bromide, potassium bromide and potassium thiocyanate can be mentioned.

The compounds of the formula (I) have the same stereo-chemistry as the known cephalosporin antibiotics. That is, the side chain at 7-position has a ß-configuration (6R,7R), while the oxyimino group in the side chains may be in either a *syn*- or *anti*-form, or as a mixture thereof. Thus, the compounds of the present invention are prepared in either form by employing the 2-(heterocyclic)-2-oxyimino-acetic acid in the *syn*- or *anti*-form and coupling reagents. Instead, separation and purification of the compounds of the formula (I) can be performed by means of recry-stallization, column chromatography, or ion exchange chromatography.

The present invention also provides a pharmaceutical composition comprising, as an active ingredient, one or more of the compounds of the formula (I) according to the present invention, a non-toxic salt, physiologically hydrolyzable ester or solvate thereof, in association with pharmaceutically acceptable carriers, excipients, or other additives.

The antibiotic compounds of the formula (I), as well as a non-toxic salt, physiologically hydrolyzable ester or solvate thereof may be formulated for administration, which may be presented in an unit dose form or in a multidose container. The formulation may be in various forms such as solutions, suspensions, or emulsions in oily or aqueous vehicles, which can contain conventional additives such as dispersing agents, suspending agents, stabilizing agents, and the like. In addition, the compounds of the present invention may be formulated into a dried powder that can be normally dissolved in an aqueous solution of sterile, pyrogen-free water, prior to use. The compounds of the present invention may also be formulated into a suppository containing conventional suppository bases such as cocoa and other glycerides.

PREFERRED EMBODIMENT OF THE INVENTION

The present invention will be described in greater detail by way of the following examples. The examples are presented for illustration purpose only and should not be construed as limiting the invention which is properly delineated in the claims.

PREPARATION 1: PREPARATION OF 2,3(1H,4H)-DIOXO-PYRAZINO-[5,6-c]PYRIDINE

To a solution of 4 g of 3,4-diaminopyridine in 120 ml of methanol, 4.36 g of sodium methoxide was added, and the mixture was stirred at room temperature for 30 minutes. A solution of 4.3 g of dimethyloxalate in 40 ml of methanol was added dropwise to the mixture over 30 minutes and the resulting mixture heated to reflux for 7 hours. The mixture was concentrated under reduced pressure, diluted with 240 ml of water, and then cooled in an ice bath. The reaction mixture was adjusted to pH 6.5 with 10 % hydrochloric acid. The precipitated solids were collected by filtration, washed with water, and dried to give 4.5 g of the title compound as a white solid.

IR (KBr, cm^{-1}) : 3230; 1709; 1383.

NMR (DMSO-d_6) : 12.1(2H,s); 8.4(1H,s); 8.2(1H,d); 7.05 (1H,d).

PREPARATION 2: PREPARATION OF 1-METHYL-2,3(4H)-DIOXO-PYRAZINO[5,6-c]PYRIDINE

3-Amino-4-methylaminopyridine was reacted in the manner similar to that described in Preparation 1 to give the title compound.

IR (cm^{-1}): 3433; 1707; 1420.

NMR (DMSO-d_6): 12.1(1H,s); 8.4(1H,s); 8.3(1H,d); 7.4(1H,d); 3.5(3H,s).

PREPARATION 3: PREPARATION OF 4-METHYL-2,3(1H)-DIOXO-PYRAZINO[5,6-c]PYRIDINE

3-Methylamino-4-aminopyridine was reacted in the manner similar to that described in Preparation 1 to give the title compound.

IR (KBr, cm^{-1}): 3225; 1708; 1380.

NMR (DMSO-d_6): 8.55(1H,s); 8.26(1H,d); 7.09(1H,d); 3.53(3H,s).

PREPARATION 4: PREPARATION OF 1-ETHYL-2,3(4H)-DIOXO-PYRAZINO[5,6-c]PYRIDINE

3-Amino-4-ethylaminopyridine was reacted in the manner similar to that described in Preparation 1 to give the title compound.

IR (cm^{-1}): 1703; 1612; 1391.

NMR (DMSO-d_6): 12.1(1H,s); 8.4(1H,s); 8.3(1H,d); 7.4(1H,d); 4.0(2H,q); 1.2(3H,t).

PREPARATION 5: PREPARATION OF 1-CYCLOPROPYL-2,3(4H)-DIOXO-PYRAZINO[5,6-c]PYRIDINE

3-Amino-4-cyclopropylaminopyridine was reacted in the manner similar to that described in Preparation 1 to give the title compound.

IR (cm^{-1}): 1707; 1612; 1416.

NMR (DMSO-d_6): 12.1(1H,s); 8.4(1H,s); 8.3(1H,d); 7.4(1H,d); 3.5(1H,m); 0.5(4H,m).

PREPARATION 6: PREPARATION OF 2(1H,3H)-OXO-IMIDAZO[4,5-c]-PYRIDINE

A mixture of 3 g of 3,4-diaminopyridine, 1.65 g of urea, and 30 ml of N,N-dimethylformamide was heated to reflux for 6 hours. The reaction mixture was cooled to room temperature and stirred for 12 hours. The precipitated solids were collected by filtration and dissolved in 30 ml of methanol. The resultant solution was treated with active carbon and evaporated under reduced pressure to give 3.1 g of the title compound as a white solid.

m.p. : 315°C (decomp.)

IR (KBr, cm^{-1}) : 3125; 1717; 1630.

NMR (DMSO-d_6) : 8.14(1H,s); 8.10(1H,d, J=5.19Hz); 6.97 (1H,d, J=5.19Hz).

PREPARATION 7: PREPARATION OF 1-METHYL-2(3H)-OXO-IMIDAZO-[4,5-c]PYRIDINE

3-Amino-4-methylaminopyridine was reacted in the manner similar to that described in Preparation 6 to give the title compound.

m.p. : 263-265 °C.

IR (KBr, cm^{-1}) : 2739; 1715; 1624.

NMR (D_2O) : 8.18(1H,s); 8.13(1H,d, J=5.3Hz); 7.1(1H,d, J=5.3Hz); 3.27(3H,s).

PREPARATION 8: PREPARATION OF 1-AMINO-2(3H)-OXO-IMIDAZO-[4,5-c]PYRIDINE HYDROCHLORIDE

3-Amino-4-hydrazinopyridine was reacted in the manner similar to that described in Preparation 6 to give the title compound.

m.p. : 309-310 °C (decomp.)

IR (KBr, cm^{-1}) : 3236; 3144; 3077; 1739; 1723.

NMR (D_2O) : 7.55-8.45(2H,2d, J=6.0Hz); 8.49(1H,s); 9.50(NH,bs); 12.5(NH_2,bs).

PREPARATION 9: PREPARATION OF 1-(2-HYDROXYETHYL)-2(3H)-OXO-IMIDAZO[4,5-c]PYRIDINE

3-Amino-4-(2-hydroxyethyl)aminopyridine was reacted in the manner similar to that described in Preparation 6 to give the title compound.

IR (KBr, cm^{-1}) : 3400; 3144; 1740; 1715.

NMR (D_2O) : 7.55-8.45(2H,2d); 8.5(1H,S); 9.5(NH,bs); 3.3-3.5(4H,dd).

PREPARATION 10: PREPARATION OF 2(1H,3H)-OXO-IMIDAZO[4,5-b]-PYRIDINE

2,3-Diaminopyridine was reacted in the manner similar to that described in Preparation 6 to give the title compound.

m.p. : 270-272 °C.

IR (KBr, cm^{-1}) : 3462; 1692; 1434.

NMR (DMSO-d_6) : 11.2(1H,s); 10.71(1H.s); 7.85(1H,s, J=1.6, 5.1Hz); 7.20(1H,s, J=1.6, 7.7Hz); 3.33(3H,s).

EXAMPLE 1: SYNTHESIS OF 7-β-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-METHOXYIMINOACETAMIDO]-3-[2,3(1H,4H)-DIOXO-PYRAZINO[5,6-c]PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

To a suspension of 500 mg of 7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid in 10 ml of well-dried dichloromethane was added, in one portion, 0.80 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide at room temperature. The reaction mixture was stirred for 5 minutes at 25 °C under a nitrogen atmosphere. To the stirred solution was added by pipette 0.50 ml of iodotrimethylsilane at 0 °C, and the reaction mixture was then stirred at room temperature for 30 minutes. Thereafter, the solvent was evaporated off under reduced pressure to provide an oil. The oil was dissolved in a mixture of 10 ml of acetonitrile and 1.0 ml of tetrahydrofuran, and the solution was stirred for 5 minutes. The stirred solution was added, in one portion, to a solution of 180 mg of 2,3(1H,4H)-dioxo-pyrazino[5,6-c]pyridine silylated with 0.80 ml of N,O-bis-(trimethylsilyl)acetamide in 10 ml of acetonitrile. The reaction mixture was stirred for 3 hours at 25 °C and then added to a mixture of 1.0 ml of methanol and 2 ml of acetonitrile at 0 °C. The mixture was stirred at 0 °C for 30 minutes. The precipitated solids were collected by filtration to give a solid product. 10 Ml of water was

added to the solid, and the mixture was neutralized with saturated sodium bicarbonate solution and then concentrated. The residue was purified by chromatography over silica gel to give 100 mg of the title compound.

m.p. : 210 °C (decomp.)

IR (KBr, cm^{-1}) : 1771; 1685; 1618.

NMR (DMSO-d_6) : 9.55(1H,d); 8.5(2H,m); 7.4(1H,d); 6.9(1H,s); 5.85(1H,dd,J=6Hz); 5.1(1H,d,J=6Hz); 3.8(3H,s)

EXAMPLE 2: SYNTHESIS OF 7-ß-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-ETHOXYIMINOACETAMIDO]-3-[2,3(1H,4H)-DIOXO-PYRAZINO[5,6-c]-PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

510 Mg of 7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was suspended in 10 ml of dry dichloromethane and reacted with 0.8 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide and then 0.5 ml of iodotrimethylsilane in the same manner as described in Example 1. The reaction mixture was concentrated. The concentrate was dissolved in a mixture of 10 ml of acetonitrile and 1 ml of tetrahydrofuran to give a solution. Separately, 200 mg of 2,3(1H,4H)-dioxo-pyrazino[5,6-c]pyridine was reacted with 0.8 ml of N,O-bistrimethylsilylacetamide in 5 ml of acetonitrile to give a silylated pyridine derivative, which was then added to the solution previously obtained. The mixture was reacted at room temperature for 3 hours. Then, to the reaction mixture, 1 ml of methanol was added to effect deprotection. The precipitated solids were filtered out and purified to give 200 mg of the title compound.

m.p.: 208 °C (decomp.)

IR (cm^{-1}): 1773; 1687; 1620.

NMR (DMSO-d_6): 9.55(1H,d); 8.5(2H,m); 7.4(1H,d); 6.9(1H,s); 5.85(1H,dd,J=6Hz);

5.1(1H,d,J=6Hz); 4.4(2H,q); 1.4(3H,t).

EXAMPLE 3: SYNTHESIS OF 7-ß-[(Z)-2-AMINOTHIAZOL-4-YL)-2-PROPYNYLOXYIMINOACETAMIDO]-3-[2,3(1H,4H)-DIOXO-PYRAZINO-[5,6-c]PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

500 Mg of 7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-propynyloxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was suspended in 10 ml of dry dichloromethane and reacted with 0.8 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide and then 0.5 ml of iodotrimethylsilane in the same manner as described in Example 1. The reaction mixture was concentrated. The concentrate was dissolved in a mixture of 10 ml of acetonitrile and 1 ml tetrahydrofuran to give a solution. Separately, 200 mg of 2,3(1H,4H)-dioxo-pyrazino[5,6-c]pyridine was reacted with 0.8 ml of N,O-bistrimethylsilylacetamide in 5 ml of acetonitrile to give a silylated pyridine derivative, which was then added to the solution previously obtained. The mixture was reacted at room temperature for 3 hours. Then, to the reaction mixture, 1 ml of methanol was added to effect deprotection. The precipitated solids were filtered out and purified to give 210 mg of the desired compound.

m.p.: 220 °C (decomp.)

IR (cm^{-1}): 1773; 1690; 1620.

NMR (DMSO-d_6): 9.6(1H,d); 8.55(2H,m); 7.4(1H,d); 6.9(1H,s); 5.8(1H,dd,J=6Hz); 5.1(1H, d,J=6Hz); 4.7(2H,m)

EXAMPLE 4: SYNTHESIS OF 7-ß-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-CYCLOPROPYLMETHOXYIMINOACETAMIDO]-3-[2,3(1H,4H)-DIOXO-PYRAZINO[5,6-c]PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

540 Mg of 7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-cyclopropylmethoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-

carboxylic acid was suspended in 10 ml of dry dichloromethane and reacted with 0.8 ml of N-methyl-N-(trimethylsilyl)-trifluoroacetamide and then 0.5 ml of iodotrimethylsilane in the same manner as described in Example 1. The reaction mixture was concentrated. The concentrate was dissolved in a mixture of 10 ml of acetonitrile and 1 ml tetrahydrofuran to give a solution. Separately, 200 mg of 2,3(1H,4H)-dioxo-pyrazino[5,6-c]pyridine was reacted with 0.8 ml of N,O-bistrimethylsilylacetamide in 5 ml of acetonitrile to give a silylated pyridine derivative, which was then added to the solution previously obtained. The mixture was reacted at room temperature for 3 hours. Then, to the reaction mixture, 1 ml of methanol was added to effect deprotection. The precipitated solids were filtered out and purified to give 230 mg of the title compound.

m.p.: 215 °C (decomp.)

IR (cm^{-1}): 1774; 1690.

NMR (DMSO-d_6): 9.6(1H,d); 8.55(2H,m); 7.4(1H,d); 6.9(1H,s); 5.8(1H,dd,J=6Hz); 5.1(1H, d,J=6Hz); 4.3(2H,d); 0.5-1.0(4H,m).

EXAMPLE 5: SYNTHESIS OF 7-β-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-CARBOXYMETHOXYIMINOACETAMIDO]-3-[2,3(1H,4H)-DIOXO-PYRAZINO-[5,6-c]PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

530 Mg of 7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was suspended in 15 ml of dry dichloromethane and reacted with 1 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide and then 0.5 ml of iodotrimethylsilane in the same manner as described in Example 1. The reaction mixture was concentrated. The concentrate was dissolved in a mixture of 15 ml of acetonitrile and 1 ml of tetrahydrofuran to give a solution. Separately, 200 mg of 2,3(1H,4H)-dioxo-pyrazino[5,6-c]pyridine was reacted with

0.8 ml of N,O-bistrimethylsilylacetamide in 5 ml of acetonitrile to give a silylated pyridine derivative, which was then added to the solution previously obtained. The mixture was reacted at room temperature for 3 hours. Then, to the reaction mixture, 1 ml of methanol was added to effect deprotection. The precipitated solids were filtered out and purified to give 250 mg of the title compound.

m.p.: 218 °C (decomp.)

IR(cm^{-1}): 1772; 1687.

NMR(DMSO-d_6): 9.6(1H,d); 8.5(2H,m); 7.4(1H,d); 6.9 (1H,s); 5.8(1H,dd,J=6Hz); 5.1(1H,d, J=6Hz); 4.6(2H,s).

EXAMPLE 6: SYNTHESIS OF 7-ß-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-(2-CARBOXYPROP-2-YL)OXYIMINOACETAMIDO]-3-[2,3(1H,4H)-DIOXO-PYRAZINO[5,6-c]PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

560 Mg of 7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-yl)oxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was suspended in 15 ml of dry dichloromethane and reacted with 1 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide and then 0.5 ml of iodotrimethylsilane in the same manner as described in Example 1. The reaction mixture was concentrated. The concentrate was dissolved in a mixture of 15 ml of acetonitrile and 1 ml of tetrahydrofuran to give a solution. Separately, 200 mg of 2,3(1H,4H)-dioxo-pyrazino[5,6-c]pyridine was reacted with 0.8 ml of N,O-bistrimethylsilylacetamide in 5 ml of acetonitrile to give a silylated pyridine derivative, which was then added to the solution previously obtained. The mixture was reacted at room temperature for 3 hours. Then, to the reaction mixture, 1 ml of methanol was added to effect deprotection. The precipitated solids

were filtered out and purified to give 250 mg of the title compound.

m.p.: 220 °C (decomp.)

IR(cm^{-1}): 1773; 1692.

NMR(DMSO-d_6): 9.55(1H,d); 8.55(2H,m); 7.4(1H,d); 6.9 (1H,s); 5.8(1H,dd,J=6Hz); 5.1(1H,d, J=6Hz); 1.5(6H,s).

EXAMPLE 7: SYNTHESIS OF 7-β-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-METHOXYIMINOACETAMIDO]-3-[1-METHYL-2,3(4H)-DIOXO-PYRAZINO[5,6-c]PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

500 Mg of 7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was suspended in 10 ml of dry dichloromethane was reacted with 0.8 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide and then 0.5 ml of iodotrimethylsilane in the same manner as described in Example 1. The reaction mixture was concentrated. The concentrate was dissolved in a mixture of 10 ml of acetonitrile and 1 ml of tetrahydrofuran to give a solution. Separately, 240 mg of 1-methyl-2,3(4H)-dioxo-pyrazino[5,6-c]pyridine was reacted with 0.8 ml of N,O-bistrimethylsilylacetamide in 5 ml of acetonitrile to give a silylated pyridine derivative, which was then added to the solution previously obtained. The mixture was reacted at room temperature for 3 hours. Then, to the reaction mixture, 1 ml of methanol was added to effect deprotection. The precipitated solids were filtered out and purified to give 250 mg of the title compound.

m.p.: 205 °C (decomp.)

IR(cm^{-1}): 1775; 1714.

NMR(DMSO-d_6): 9.6(1H,d); 8.5(2H,m); 7.4(1H,d); 6.9 (1H,s); 5.8(1H,dd,J=6Hz); 5.15(1H,d, J=6Hz); 3.8(3H,s); 3.5(3H,s).

EXAMPLE 8: SYNTHESIS OF 7-ß-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-METHOXYIMINOACETAMIDO]-3-[1-ETHYL-2,3(4H)-DIOXO-PYRAZINO-[5,6-c]PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

500 Mg of 7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was suspended in 10 ml of dry dichloromethane and reacted with 0.8 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide and then 0.5 ml of iodotrimethylsilane in the same manner as described in Example 1. The reaction mixtue was concentrated. The concentrate was dissolved in a mixture of 10 ml of acetonitrile and 1 ml of tetrahydrofuran to give a solution. Separately, 250 mg of 1-ethyl-2,3(4H)-dioxo-pyrazino[5,6-c]pyridine was reacted with 0.8 ml of N,O-bistrimethylsilylacetamide in 5 ml of acetonitrile to give a silylated pyridine derivative, which was then added to the solution previously obtained. The mixture was reacted at room temperature for 3 hours. Then, to the reaction mixture, 1 ml of methanol was added to effect deprotection. The precipitated solids were filtered out and purified to give 250 mg of the title compound.

m.p.: 210 °C (decomp.)

IR(cm^{-1}): 1775; 1716.

NMR(DMSO-d_6): 9.6(1H,d); 8.5(2H,m); 7.4(1H,d); 6.9 (1H,s); 5.8(1H,dd,J=6Hz); 5.2(1H,d, J=6Hz); 3.8(3H,s); 4.0(2H,q); 1.2(3H,t).

EXAMPLE 9: SYNTHESIS OF 7-ß-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-METHOXYIMINOACETAMIDO]-3-[1-CYCLOPROPYL-2,3(4H)-DIOXO-PYRAZINO[5,6-c]PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

500 Mg of 7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was suspended in 10 ml of dry dichloromethane was

reacted with 0.8 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide and then 0.5 ml of iodotrimethylsilane in the same manner as described in Example 1. The reaction mixture was concentrated. The concentrate was dissolved in a mixture of 10 ml of acetonitrile and 1 ml of tetrahydrofuran to give a solution. Separately, 270 mg of 1-cyclopropyl-2,3(4H)-dioxo-pyrazino[5,6-c]pyridine was reacted with 0.8 ml of N,O-bistrimethylsilylacetamide in 5 ml of acetonitrile to give a silylated pyridine derivative, which was then added to the solution previously obtained. The mixture was reacted at room temperature for 3 hours. Then, to the reaction mixture, 1 ml of methanol was added to effect deprotection. The precipitated solids were filtered out and purified to give 230 mg of the title compound.

m.p.: 208 °C(decomp.)

IR(cm^{-1}): 1774; 1716.

NMR(DMSO-d_6): 9.6(1H,d); 8.5(2H,m); 7.4(1H,d); 6.9 (1H,s); 5.8(1H,dd,J=6Hz); 5.2(1H,d, J=6Hz); 3.8(3H,s); 3.5(1H,m), 0.6(4H,m).

EXAMPLE 10: SYNTHESIS OF 7-β-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-(2-CARBOXYPROP-2-YL)OXYIMINOACETAMIDO]-3-[1-METHYL-2,3(4H)-DIOXO-PYRAZINO[5,6-c]PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

560 Mg of 7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-yl)oxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was suspended in 15 ml of dry dichloromethane and reacted with 1 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide and then 0.5 ml of iodotrimethylsilane in the same manner as described in Example 1. The reaction mixture was concentrated. The concentrate was dissolved in a mixture of 15 ml of acetonitrile and 1 ml of tetrahydrofuran to give a solution. Separately, 240 mg

of 1-methyl-2,3(4H)-dioxo-pyrazino[5,6-c]pyridine was reacted with 0.8 ml of N,O-bistrimethylsilylacetamide in 5 ml of acetonitrile to give a silylated pyridine derivative, which was then added to the solution previously obtained. The mixture was reacted at room temperature for 3 hours. Then, to the reaction mixture, 2 ml of methanol was added to effect deprotection. The precipitated solids were filtered out and purified to give 200 mg of the title compound.

m.p.: 215 °C (decomp.)

IR(cm^{-1}): 1773; 1715.

NMR(DMSO-d_6): 9.6(1H,d); 8.55(2H,m); 7.4(1H,d); 6.9 (1H,s); 5.8(1H,dd,J=6Hz); 5.2(1H,d, J=6Hz); 3.5(3H,s); 1.5(6H,s).

EXAMPLE 11: SYNTHESIS OF 7-ß-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-(2-CARBOXYPROP-2-YL)OXYIMINOACETAMIDO]-3-[1-ETHYL-2,3(4H)-DIOXO-PYRAZINO[5,6-c]PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

560 Mg of 7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-yl)oxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was suspended in 15 ml of dry dichloromethane and reacted with 1 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide and then 0.5 ml of iodotrimethylsilane in the same manner as described in Example 1. The reaction mixture was concentrated. The concentrate was dissolved in a mixture of 15 ml of acetonitrile and 1 ml of tetrahydrofuran to give a solution. Separately, 250 mg of 1-ethyl-2,3(4H)-dioxo-pyrazino[5,6-c]pyridine was reacted with 0.8 ml of N,O-bistrimethylsilylacetamide in 5 ml of acetonitrile to give a silylated pyridine derivative, which was then added to the solution previously obtained. The mixture was reacted at room temperature for 3 hours. Then, to the reaction mixture, 2 ml of methanol

was added to effect deprotection. The precipitated solids were filtered out and purified to give 230 mg of the title compound.

m.p.: 217 °C (decomp.)

IR(cm^{-1}): 1774; 1717.

NMR(DMSO-d_6): 9.6(1H,d); 8.5(2H,m); 7.4(1H,d); 6.9 (1H,s); 5.8(1H,dd,J=6Hz); 5.2(1H,d, J=6Hz); 4.0(2H,q); 1.5(6H,s); 1.2(3H,t).

EXAMPLE 12: SYNTHESIS OF 7-ß-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-(2-CARBOXYPROP-2-YL)OXYIMINOACETAMIDO]-3-[1-CYCLOPROPYL-2,3(4H)-DIOXO-PYRAZINO[5,6-c]PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

560 Mg of 7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-yl)oxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was suspended in 15 ml of dry dichloromethane and reacted with 1 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide and then 0.5 ml of iodotrimethylsilane in the same manner as described in Example 1. The reaction mixture was concentrated. The concentrate was dissolved in a mixture of 15 ml of acetonitrile and 1 ml of tetrahydrofuran to give a solution. Separately, 270 mg of 1-cyclopropyl-2,3(4H)-dioxo-pyrazino[5,6-c]pyridine was reacted with 0.8 ml of N,O-bistrimethylsilylacetamide in 5 ml of acetonitrile to give a silylated pyridine derivative, which was then added to the solution previously obtained. The mixture was reacted at room temperature for 3 hours. Then, to the reaction mixture, 2 ml of methanol was added to effect deprotection. The precipitated solids were filtered out and purified to give 250 mg of the title compound.

m.p.: 215 °C (decomp.)

IR(cm^{-1}): 1775; 1716.

NMR(DMSO-d_6): 9.6(1H,d); 8.5(2H,m); 7.4(1H,d);

6.9(1H,s); 5.8(1H,dd,J=6Hz); 5.2(1H,d, J=6Hz); 3.5(1H,m); 1.5(6H,s); 0.6(4H,m).

EXAMPLE 13: SYNTHESIS OF 7-β-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-METHOXYIMINOACETAMIDO]-3-[4-METHYL-2,3(1H)-DIOXO-PYRAZINO[5,6-c]PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

To a suspension of 340 mg of 7-β-[(z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid in 10 ml of dry dichloromethane was added, in one portion, 0.5 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide at room temperature. The reaction mixture was stirred for 5 minutes at 25 °C under a nitrogen atmosphere. To the stirred solution was added 0.24 ml of iodotrimethylsilane at 0 °C and the reaction mixture was then stirred at room temperature for 30 minutes. The solvent was removed by evaporation under reduced pressure to give an oil. The oil was dissolved in a mixture of 10 ml of acetonitrile and 1 ml of tetrahydrofuran. The resultant solution was stirred for 5 minutes. The stirred solution was added, in one portion, to a solution of 4-methyl-2,3(1H)-dioxo-pyrazino[5,6-c]pyridine silylated with 0.8 ml of N,O-bis(trimethylsilyl)acetamide in 10 ml of acetonitrile. The reaction mixture was stirred for 3 hours at 25 °C and then added to a mixture of 1.0 ml of methanol and 2 ml of acetonitrile at 0 °C. The precipitated solids were collected by filtration to give a solid product. 10 Ml of water was added to the solid, and the mixture was neutralized with a saturated $NaHCO_3$ solution and then concentrated. The resultant residue was purified by chromatography over silica gel eluting with acetonitrile:H_2O (4:1) and concentrated to give 40 mg of the title compound.

m.p.: 220 °C (decomp.)

IR (KBr, cm^{-1}): 1760; 1620.

NMR (DMSO-d_6): 9.7(1H,d,J=7.8Hz); 8.5(1H,s); 8.3 (1H,d); 7.10(1H,d); 6.8(1H,s); 5.6 (1H,dd, J=7.8, 4.5Hz); 5.1(1H,d, J=4.86Hz); 4.9(2H,bs); 3.75(3H,s); 3.5 (3H,s); 3.4(2H,m).

EXAMPLE 14: SYNTHESIS OF 7-ß-[(Z)-2-(AMINOTHIAZOL-4-YL)-2-FLUOROMETHOXYIMINOACETAMIDO]-3-[2,3(1H,4H)-DIOXO-PYRAZINO-[5,6-c]PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

To a suspension of 700 mg of 7-ß-[(z)-2-(2-amino-thiazol-4-yl)-2-fluoromethoxyiminoacetamido]-3-acetoxy-methyl-3-cephem-4-carboxylic acid in 15 ml of dry dichloro-methane was added, in one portion, 1.0 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide at room temperature. The reaction mixture was stirred for 5 minutes at 25 °C under a nitrogen atmosphere. To the stirred solution was added by pipette 0.44 ml of iodotrimethylsilane at 0 °C, and the reaction mixture was then stirred at room temperature for 30 minutes. Thereafter, the mixture was evaporated under reduced pressure to remove the solvent and then provide an oil. The oil was dissolved in a mixture of 10 ml of acetonitrile and 1.0 ml of tetrahydrofuran, and the solution was stirred for 5 minutes. The stirred solution was added in one portion to a solution of 400 mg of 2,3(1H,4H)-dioxo-pyrazino[5,6-c]pyridine silylated with 0.88 ml of N,O-bis(trimethylsilyl)acetamide in 10 ml of acetonitrile. The reaction mixture was stirred for 3 hours at 25 °C and then added to a mixture of 1.0 ml of methanol and 2 ml of acetonitrile at 0 °C. The mixture was stirred at 0 °C for 30 minutes. The precipitated solids were collected by filtration to give a solid product. 10 Ml of water was added to the solid, and the mixture was neutralized with a saturated sodium bicarbonate solution and then concentrated. The residue was purified by

chromatography over silica gel to give 250 mg of the title compound.

m.p.: 220 °C (decomp.)

IR (KBr, cm^{-1}) 1770; 1688; 1619.

NMR (DMSO-d_6): 9.72(1H,bd,J=7.84Hz); 8.51(1H,s); 8.35 (1H,bs); 7.10(1H,d,J=5.7Hz); 6.88 (1H,s); 6.32(2H,d,J=55.18Hz); 5.65 (1H,dd, J=7.84, 4.87Hz); 5.05(1H,d, J=4.87Hz); 4.95(2H,bs); 3.44(2H,m).

EXAMPLE 15: SYNTHESIS OF 7-ß-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-METHOXYIMINOACETAMIDO]-3-[2(1H,3H)-OXO-IMIDAZO[4,5-c]-PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

To a suspension of 500 mg of 7-ß-[(Z)-2-(2-amino-thiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid in 10 ml of dry dichloromethane was added, in one portion, 0.7 ml of N-methyl-N-(trimethyl-sily)trifluoroacetamide at room temperature. The reaction mixture was stirred for 5 minutes at 25 °C under a nitrogen atmosphere. To the stirred solution was added by pipette 0.38 ml of iodotrimethylsilane at 0 °C, and the reaction mixture was then stirred at room temperature for 30 minutes. Thereafter, the reaction mixture was evaporated under reduced pressure to remove the solvent and then give an oil. The oil was dissolved in a mixture of 10 ml of acetonitrile and 1 ml of tetrahydrofuran. The resultant solution was stirred for 5 minutes. The stirred solution was added, in one portion, to a solution of 10 mg of 2(1H,3H)-oxo-imidazo[4,5-c]pyridine silylated with 0.62 ml of N,O-bis(trimethylsilyl)acetamide in 10 ml of aceto-nitrile. The reaction mixture was stirred for 3 hours at 25 °C and then added to a mixture of 0.5 ml of methanol and 5 ml of acetonitrile at 0 °C. The precipitated solids were collected by filtration to provide a solid product. 10 Ml

of water was added to the solid, and the mixture was neutralized with a saturated $NaHCO_3$ solution and then concentrated. The resultant residue was purified by chromatography over silica gel eluting with acetonitrile: H_2O (4:1) and concentrated to give 170 mg of the title compound.

m.p. : 219 °C (decomp.)

IR(KBr, cm^{-1}) : 1772, 1653, 1636.

NMR (DMSO-d_6) : 3.18(1H,d, J=17.1Hz); 3.53(1H, m); 3.58(1H,d, J=17.1Hz); 3.78(3H,s); 4.77(1H,m); 5.06(1H,d); 5.61(1H,dd); 6.70(1H,s); 7.18(1H,bd,J=6.85Hz); 8.48(1H,bd, J=6.85Hz); 8.85(1H,s); 9.48(1H,dd).

EXAMPLE 16: SYNTHESIS OF 7-ß-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-METHOXYIMINOACETAMIDO]-3-[1-METHYL-2(3H)-OXO-IMIDAZO[4,5-c]PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

To a suspension of 450 mg of 7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid in 10 ml of dry dichloromethane was added, in one portion, 0.5 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide at room temperature. The reaction mixture was stirred for 5 minutes at 25 °C under a nitrogen atmosphere. To the stirred solution was added by pipette 0.24 ml of iodotrimethylsilane at 0 °C, and the reaction mixture was then stirred at room temperature for 30 minutes. Thereafter, the mixture was evaporated under reduced pressure to remove the solvent and then give an oil. The oil was dissolved in a mixture of 10 ml of acetonitrile and 1 ml of tetrahydrofuran. The resultant solution was stirred for 5 minutes. The stirred solution was added, in one portion, to a solution of 90 mg of 1-methyl-2(3H)-oxo-imidazo[4,5-c]pyridine silylated with 0.5

ml of N,O-bis(trimethylsily)acetamide in 10 ml of acetonitrile. The reaction mixture was stirred for 3 hours at 25 °C and then added to a mixture of 0.5 ml of methanol and 5 ml of acetonitrile at 0 °C. The mixture was stirred at 0 °C for 30 minutes. The precipitated solids were collected by filtration to give a solid product. 10 Ml of water was added to the solid, and the mixture was neutralized with a saturated sodium bicarbonate solution and then concentrated. The residue was purified by chromatography over silica gel to give 50 mg of the title compound.

m.p. : 250 °C (decomp.)

IR (KBr, cm^{-1}) : 1760; 1616; 1590.

NMR (D_2O) : 8.34(1H,s); 8.1(1H,s); 7.35(1H,d); 7.00(1H,s); 5.9(1H,d); 5.15(1H,d); 4.60(2H,q); 3.80(2H,q); 3.35(2H,q); 3.15(3H,s).

EXAMPLE 17: SYNTHESIS OF 7-β-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-METHOXYIMINOACETAMIDO]-3-[1-AMINO-2(3H)-OXO-IMIDAZO[4,5-c]PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

To a suspension of 650 mg of 7-β-[(z)-2-(aminothiazol-4-ly)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid in 15 ml of dry dichloromethane was added, in one portion, 7.8 ml of N-methyl-N-(trimethylsily)trifluoroacetamide at room temperature. The reaction mixture was stirred for 5 minutes at 25 °C under a nitrogen atmosphere. To the stirred solution were added by pipette 0.49 ml of iodotrimethylsilane at 0 °C, and the reaction mixture was then stirred at room temperature for 30 minutes. Thereafter, the mixture was evaporated under reduced pressure to remove the solvent and then give an oil. The oil was dissolved in a mixture of 10 ml of acetonitrile and 1 ml of tetrahydrofuran, and the resulting

solution was stirred for 5 minutes. The stirred solution was added, in one portion, to a solution of 165 mg of 1-amino-2(3H)-oxo-imidazo[4,5-c]pyridine silylated with 8.2 ml of N,O-bis(trimethylsilyl)acetamide in 10 ml of acetonitrile. The reaction mixture was stirred for 3 hours at 25 °C and then added to a mixture of 0.5 ml of methanol and 5 ml of acetonitrile at 0 °C. The mixture was stirred at 0 °C for 30 minutes. The precipitated solids were collected by filtration to give a solid product. 10 Ml of water was added to the solid and the mixture was neutralized with a saturated sodium bicarbonate solution and then concentrated. The residue was purified by chromatography over silica gel to give 120 mg of the title compound.

m.p. : 224 °C (decomp.)

IR (KBr, cm^{-1}) : 1785; 1653.

NMR (DMSO-d_6) : 9.6(1H,d, J=7.6Hz); 8.9(1H,s); 8.6(1H,d, J=6.6Hz); 7.5(1H,d, J=6.6Hz); 7.2(2H,b); 6.7(1H,m); 6.6(2H,bd); 5.8(1H,dd, J=7.8, 5.0Hz); 5.1(1H,d, J=5.0Hz); 5.4(2H,bd); 3.8(3H,s); 3.4(2H,m).

EXAMPLE 18: SYNTHESIS OF 7-β-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-METHOXYIMINOACETAMIDO]-3-[1-(2-HYDROXYETHYL)-2(3H)-OXO-IMIDAZO[4,5-c]PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

To a suspension of 700 mg of 7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid in 70 ml of dry dichloromethane was added, in one portion, 16 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide at room temperature. The reaction mixture was stirred for 5 minutes at 25 °C under a nitrogen atmosphere. To the stirred solution was added by pipette 0.5 ml of iodotrimethylsilane at 0 °C, and the reaction mixture was then stirred at room temperature for 30

minutes. Thereafter, the mixture was evaporated under reduced pressure to remove the solvent and then give an oil. The oil was dissolved in a mixture of 10 ml of acetonitrile and 1 ml of tetrahydrofuran, and the solution was stirred for 5 minutes. The stirred solution was added, in one portion, to a solution of 160 mg of 1-(2-hydroxyethyl)-2(3H)-oxo-imidazo[4,5-c]pyridine silylated with 8.3 ml of N,O-bis(trimethylsilyl)acetamide in 10 ml of acetonitrile. The reaction mixture was stirred for 3 hours at 25 °C and then added to a mixture of 0.6 ml of methanol and 6 ml of acetonitrile at 0°C. The mixture was stirred at 0 °C for 30 minutes. The precipitated solids were collected by filtration to give a solid product. 70 Ml of water was added to the solid, and the mixture was neutralized with a saturated sodium bicarbonate solution and then concentrated. The residue was purified by chromatography over silica gel to give 115 mg of the title compound.

m.p. : 250 °C

NMR : 9.5(1H,d); 8.7(1H,s); 8.5(1H,d); 7.4(1H,d); 7.1(1H,s); 6.7(1H,s); 5.6(1H,dd); 5.1(1H,d); 3.75(3H,s); 3.0-3.6(4H,m)

EXAMPLE 19: SYNTHESIS OF 7-ß-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-METHOXYIMINOACETAMIDO]-3-[2(1H,3H)-OXO-IMIDAZO[4,5-b]-PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

To a suspension of 500mg of 7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid in 10 ml of dry dichloromethane was added, in one portion, 0.74 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide at room temperature. The reaction mixture was stirred for 5 minutes at 25 °C under a nitrogen atmosphere. To the stirred solution was added by pipette 0.39 ml of iodotrimethylsilane at 0 °C, and the reaction mixture was then stirred at room temperature for

30 minutes. Thereafter, the solvent was evaporated off under reduced pressure to give an oil. The oil was dissolved in a mixture of 15 ml of acetonitrile and 0.5 ml of tetrahydrofuran, and the solution was stirred for 5 minutes. The stirred solution was added, in one portion, to a solution of 150 mg of 2(1H,3H)-oxo-imidazo[4.5-b]-pyridine silylated with 1.1 ml of N,O-bis(trimethylsily)-acetamide in 3 ml of acetonitrile. The reaction mixture was stirred for 3 hours at 25 °C and then added to a mixture of 0.5 ml of methanol and 5 ml of acetonitrile at 0°C. The mixture was stirred at 0°C for 30 minutes. The precipitated solids were collected by filtration to give a solid product. 10 Ml of water was added to the solid, and the mixture was neutralized with a saturated sodium bicarbonate solution and then concentrated. The residue was purified by chromatography over silica gel to give 110 mg of the title compound.

m.p. : 256°C (decomp.)

IR (KBr, cm^{-1}) : 1668; 1769.

NMR (D_2O) : 3.3(2H,q); 3.95(3H,s); 4.66(2H,q); 5.2(1H,d, J=4.9Hz); 6.96(1H,m); 6.9(1H,s); 7.4(1H,d, J=7.4Hz); 7.75(1H,d, J=5.4Hz).

EXAMPLE 20: SYNTHESIS OF 7-ß-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-FLUOROMETHOXYIMINOACETAMIDO]-3-[2(1H,3H)-OXO-IMIDAZO-[4,5-c]PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

To a suspension of 700 mg of 7-ß-[(Z)-2-(2-amino-thiazol-4-yl)-2-fluoromethoxyiminoacetamido]-3-acetoxy-methyl-3-cephem-4-carboxylic acid in 15 ml of dry dichloro-methane was added, in one portion, 1.0 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide at room temperature. The reaction mixture was stirred for 5 minutes at 25 °C under a nitrogen atmosphere. To the stirred solution was added by pipette 0.44 ml of iodotrimethylsilane at 0 °C,

and the reaction mixture was then stirred at room temperature for 30 minutes. Thereafter, the mixture was evaporated under reduced pressure to remove the solvent and then give an oil. The oil was dissolved in a mixture of 10 ml of acetonitrile and 1.0 ml of tetrahydrofuran, and the solution was stirred for 5 minutes. The stirred solution was added in one portion to a solution of 178 mg of 2(1H,3H)-oxo-imidazo[4,5-c]pyridine silylated with 0.88 ml of N,O-bis(trimethylsily)acetamide in 10 ml of acetonitrile. The reaction mixture was stirred for 3 hours at 25 °C and then added to a mixture of 1.0 ml of methanol and 2 ml of acetonitrile at 0 °C. The mixture was stirred at 0 °C for 30 minutes. The precipitated solids were collected by filtration to give a solid product. 10 Ml of water was added to the solid, and the mixture was neutralized with a saturated sodium bicarbonate solution and then concentrated. The residue was purified by chromatography over silica gel to give 110 mg of the title compound.

m.p. : 210°C (decomp.)

IR (KBr, cm^{-1}) : 1763; 1653; 1616.

NMR (D_2O) : 3.18(1H,d); 3.58(1H,d); 4.41(1H,s); 4.99 (1H,s); 5.30(1H,d, J=4.80Hz); 5.81(2H,d, J=55.07Hz); 5.88(1H,d, J=4.80Hz); 7.15 (1H,s); 7.46(1H,d, J=6.9Hz); 8.35(1H,d, J=6.9Hz); 8.46(1H,s).

EXAMPLE 21: SYNTHESIS OF 7-ß-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-FLUOROMETHOXYIMINOACETAMIDO]-3-[1-METHYL-2(3H)-OXO-IMIDAZO[4,5-c]PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

To a suspension of 300 mg of 7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-fluoroemthoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid in 5 ml of dry dichloromethane was added, in one portion, 0.5 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide at room temperature.

The reaction mixture was stirred for 5 minutes at 25 °C under a nitrogen atmosphere. To the stirred solution was added by pipette 0.3 ml of iodotrimethylsilane at 0 °C, and the reaction mixture was then stirred at room temperature for 30 minutes. Thereafter, the solvent was evaporated off under reduced pressure to give an oil. The oil was dissolved in a mixture of 10 ml of acetonitrile and 0.5 ml of tetrahydrofuran, and the resultant solution was stirred for 5 minutes. The stirred solution was then added, in one portion, to a solution of 85 mg of 1-methyl-2(3H)-oxo-imidazo[4,5-c]pyridine silylated with 0.71 ml of N,O-bis-(trimethylsilyl)acetamide in 3 ml of acetonitrile. The reaction mixture was stirred for 3 hours at 25 °C and then added to a mixture of 0.3 ml of methanol and 2 ml of acetonitrile at 0 °C. The mixture was stirred at 0°C for 30 minutes. The precipitated solids were collected by filtration to give a solid product. 10 Ml of water was added to the solid, and the mixture was neutralized with a saturated sodium bicarbonate solution and then concentrated. The residue was purified by chromatography over silica gel to give 60 mg of the title compound.

m.p. : 242 °C (decomp.)

IR (KBr, cm^{-1}) : 1533; 1616; 1751.

NMR (D_2O) : 8.35(1H,s); 8.2(1H,s); 7.35(1H,d); 7.06 (1H,s); 5.78(2H,d, J=55.4Hz); 5.85(1H,d); 5.3(1H,d); 4.55 (2H,q); 3.35(2H,q).

EXAMPLE 22: SYNTHESIS OF 7-ß-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-FLUOROMETHOXYIMINOACETAMIDO]-3-[1-AMINO-2(3H)-OXO-IMIDAZO[4,5-c]PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

To a suspension of 500 mg of 7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-fluoromethoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid in 10 ml of dry dichloromethane was added, in one portion, 0.65 ml of N-methyl-N-

(trimethylsilyl)trifluoroacetamide at room temperature. The reaction mixture was stirred for 5 minutes at 25 °C under a nitrogen atmosphere. To the stirred solution was added by pipette 0.45 ml of iodotrimethylsilane at 0 °C, and the reaction mixture was then stirred at room temperature for 30 minutes. Thereafter, the solvent was evaporated off under reduced pressure to give an oil. The oil was dissolved in a mixture of 10 ml of acetonitrile and 1.0 ml of tetrahydrofuran, and the solution was stirred for 5 minutes. The stirred solution was added, in one portion, to a solution of 160 mg of 1-amino-2(3H)-oxo-imidazo[4,5-c]pyridine silylated with 0.71 ml of N,O-bis(trimethylsily)acetamide in 10 ml of acetonitrile. The reaction mixture was stirred for 3 hours at 25 °C and then added to a mixture of 1.0 ml of methanol and 2 ml of acetonitrile at 0 °C. The mixture was stirred at 0 °C for 30 minutes. The precipitated solids were collected by filtration to give a solid product. 10 Ml of water was added to the solid and the mixture was neutralized with a saturated sodium bicarbonate solution and then concentrated. The residue was purified by chromatography over silica gel to give 105 mg of the title compound.

m.p. : 215 °C (decomp.)

IR (KBr, cm^{-1}) : 1773; 1654.

NMR (DMSO-d_6) : 9.75(1H,d); 8.65(1H,s); 8.55(1H,d, J=6.7Hz); 7.65(1H,d, J=6.7Hz); 7.2 (2H,m); 6.9(1H,s); 5.8 (1H,m); 5.6 (2H,d, J=55.0Hz); 5.4(2H,bd); 5.15 (1H,d); 3.4(2H,m).

EXAMPLE 23: SYNTHESIS OF 7-ß-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-FLUOROMETHOXYIMINOACETAMIDO]-3-[2(1H,3H)-OXO-IMIDAZO-[4,5-b]PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

To a suspension of 300 mg of 7-ß-[(Z)-2-(2-aminothia-

zol-4-yl)-2-fluoromethoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid in 10 ml of dry dichloromethane was added, in one portion, 0.55 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide at room temperature. The reaction mixture was stirred for 5 minutes at 25 °C under a nitrogen atmosphere. To the stirred solution was added by pipette 0.33 ml of iodotrimethylsilane at 0 °C, and the reaction mixture was then stirred at room temperature for 30 minutes. Thereafter, the solvent was evaporated off under reduced pressure to give an oil. The oil was dissolved in a mixture of 15 ml of acetonitrile and 0.3 ml of tetrahydrofuran, and the solution was stirred for 5 minutes. The stirred solution was added, in one portion, to a solution of 100 mg of 2(1H,3H)-oxo-imidazo[4,5-b]-pyridine silylated with 0.90 ml of N,O-bis(trimethylsilyl)-acetamide in 3 ml of acetonitrile. The reaction mixture was stirred for 3 hours at 25 °C and then added to a mixture of 0.5 ml of methanol and 2 ml of acetonitrile at 0 °C. The mixture was stirred at 0 °C for 30 minutes. The precipitated solids were collected by filtration to give a solid product. 10 Ml of water was added to the solid, and the mixture was neutralized with a saturated sodium bicarbonate solution and then concentrated. The residue was purified by chromatography over silica gel to give 20 mg of the title compound.

m.p. : 231 °C (decomp.)

IR (KBr, cm^{-1}) : 1616; 1668; 1767.

NMR (D_2O) : 3.40(2H,q); 4.60(2H,q); 5.25(1H,d, J=4.80Hz); 5.85(2H,d, J=55.0Hz); 5.95 (1H,d, J=4.80Hz); 7.10(1H,m); 7.15(1H,s); 7.50(1H,d); 7.75(1H,d).

EXAMPLE 24: SYNTHESIS OF 7-ß-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-CARBOXYMETHOXYIMINOACETAMIDO]-3-[2(1H,3H)-OXO-IMIDAZO-[4,5-c]PYRIDINIUMMETHYL]-3-CEPHEM-4-CARBOXYLATE

To a suspension of 700 mg of 7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid in 15 ml of dry dichloromethane was added, in one portion, 0.95 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide at room temperature. The reaction mixture was stirred for 5 minutes at 25 °C under a nitrogen atmosphere. To the stirred solution was added by pipette 0.40 ml of iodotrimethylsilane at 0 °C, and the reaction mixture was then stirred at room temperature for 30 minutes. Thereafter, the solvent was evaported off under reduced pressure to give an oil. The oil was dissolved in a mixture of 10 ml of acetonitrile and 1.0 ml of tetrahydrofuran, and the solution was stirred for 5 minutes. The stirred solution was added, in one portin, to a solution of 180 mg of 2(1H,3H)-oxo-imidazo[4,5-c]pyridine silylated with 0.80 ml of N,O-bis(trimethylsilyl)acetamide in 10 ml of acetonitrile. The reaction mixture was stirred for 3 hours at 25 °C and then added to a mixture of 1.0 ml of methanol and 2 ml of acetonitrile at 0 °C. The mixture was stirred at 0 °C for 30 minutes. The precipitated solids were collected by filtration to give a solid product. 10 Ml of water was added to the solid, and the mixture was neutralized with a saturated sodium bicarbonate solution and then concentrated. The residue was purified by chromatography over silica gel to give 80 mg of the title compound.

m.p. : 228 °C (decomp.)

IR (KBr, cm^{-1}) : 1761; 1653; 1616.

NMR (DMSO-d_6) : 3.35(1H,q); 4.50(2H,s); 4.75(2H,q); 5.25(1H,d, J=4.7Hz); 5.85(1H,d, J=4.7Hz); 6.95(1H,s); 7.45 (1H,d, J=6.7Hz); 8.35(1H,d, J=6.7Hz); 8.60 (1H,s).

The title compounds illustrated in the above Examples are summarized in Table 1 below.

Table 1

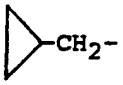
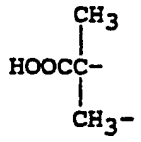
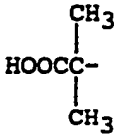
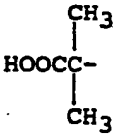
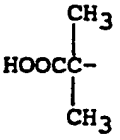
Example No.	n	R_1	R_2	R_3	Fused position
Ex. 1	2	CH_3-	H	H	3,4-fused
Ex. 2	2	CH_3CH_2-	H	H	3,4-fused
Ex. 3	2	HC C-CH_2-	H	H	3,4-fused
Ex. 4	2		H	H	3,4-fused
Ex. 5	2	$HOOCCH_2$-	H	H	3,4-fused
Ex. 6	2		H	H	3,4-fused
Ex. 7	2	CH_3-	CH_3-	H	3,4-fused
Ex. 8	2	CH_3-	CH_3CH_2-	H	3,4-fused
Ex. 9	2	CH_3-		H	3,4-fused
Ex.10	2		CH_3-	H	3,4-fused
Ex.11	2		CH_3CH_2-	H	3,4-fused
Ex.12	2			H	3,4-fused
Ex.13	2	CH_3-	H	CH_3-	3,4-fused
Ex.14	2	FCH_2-	H	H	3,4-fused

Table 1 (Continued)

Example No.	n	R_1	R_2	R_3	Fused position
Ex.15	1	CH_3-	H	H	3,4-fused
Ex.16	1	CH_3-	CH_3-	H	3,4-fused
Ex.17	1	CH_3-	H_2N-	H	3,4-fused
Ex.18	1	CH_3-	$HOCH_2CH_2$-	H	3,4-fused
Ex.19	1	CH_3-	H	H	2,3-fused
Ex.20	1	FCH_2-	H	H	3,4-fused
Ex.21	1	FCH_2-	CH_3-	H	3,4-fused
Ex.22	1	FCH_2-	H_2N-	H	3,4-fused
Ex.23	1	FCH_2-	H	H	2,3-fused
Ex.24	1	$HOOCCH_2$-	H	H	3,4-fused

INDUSTRIAL APPLICABILITY

The advantageous effects accruing from and the industrial applicability of the present invention are illustrated by means of the following experimental examples.

EXPERIMENTAL EXAMPLE 1: *in vitro* ACTIVITY

The *in vitro* antibacterial activities of several representative compounds of the present invention against various gram-positive and gram-negative microorganisms were evaluated by the following two-fold dilution method. As reference compounds, cefotaxime (CTX) and ceftazidime (CAZ) were employed.

Two-fold serial dilutions of the compounds of Examples 1, 2, 3, 5, 6, 7, 9 and 10, and the reference compounds were prepared. 1.5 Ml of each dilution and subsequently 13.5 ml of Mueller-Hinton agar were added into a test tube and then mixed together. After thoroughly mixing, the mixture was poured into a sterilized Petri dish and coagulated. Each test microorganism-diluted suspension (about 10^4 cfu/spot) was inoculated to the Mueller Hinton agar with an inoculator. After incubation at 37°C for 18 hours, the minimum inhibitory concentrations (MICs: μg/ml) of the test and the reference compounds were measured. The results are shown in Table 2 below.

Table 2

Strain		Compound of Ex. 1	Ex. 2	Ex. 3	Ex. 5	Ex. 6	Ex. 7	Ex. 9	Ex.10	CTX	CAZ
S.pyogenes	A8668	0.013	0.013	0.013	0.196	0.782	0.025	0.049	0.782	0.013	0.196
S.aureus	A29213	1.563	1.563	0.782	25	12.5	1.563	3.125	12.5	0.782	12.5
S.epidermidis	A12228	0.391	0.391	0.391	1.563	3.125	0.391	1.563	3.125	0.391	6.25
E.coli	A10536	0.007	0.013	0.013	0.002	0.007	0.007	0.025	0.007	0.013	0.098
P.mirabilis	A25933	0.013	0.025	0.013	<0.002	0.007	0.007	0.049	0.013	0.013	0.049
S.marcescens	A27117	0.025	0.049	0.049	0.004	0.007	0.007	0.782	0.013	0.049	0.391
P.aeruginosa	A10145	3.125	6.25	3.125	1.563	1.563	12.5	25	6.25	25	3.125

EXPERIMENTAL EXAMPLE 2: *in vitro* ACTIVITY

In order to further illustrate the *in vitro* antibacterial activities of other representative compounds of the present invention, the minimal inhibitory concentrations (MIC) thereof against various gram-positive and gram-negative microorganisms were determined, and compared with those of cefotaxime (CTX) and ceftazidime (CAZ). The *in vitro* antibacterial activities were determined by the two-fold dilution method similar to that described in Experimental Example 1.

The two-fold serial dilutions of the test compounds and reference compounds were made and dispersed in Muller-Hinton agar medium. Then, 2 μl of standard test strain which had 10^4 cfu/spot was inoculated on the medium, and was incubated at 37 °C for 20 hours. After the incubation, MICs (μg/ml) of the test and reference compounds were measured. The results are shown in Table 3 below.

Table 3

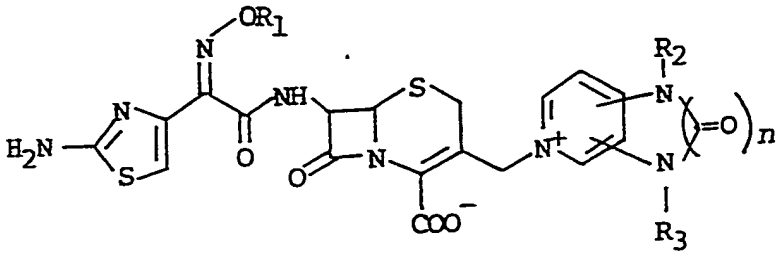
Strain		Compound of Ex.15	Ex.20	Ex.24	Ex.16	Ex.21	Ex.17	Ex.22
S.pyogenes	A8668	0.007	0.007	0.098	0.013	0.007	0.007	0.013
S.pyogenes	C4003	0.007	0.007	0.196	0.013	0.007	0.013	0.025
S.aureus	A29213	1.563	0.782	12.5	1.563	1.563	1.563	1.563
S.aureus	C4036	0.782	0.782	12.5	1.563	0.782	1.563	1.563
MRSA	C1060	25	25	50	100	25	100	50
S.epidermidis	A12228	0.391	0.391	6.25	0.391	0.391	0.391	0.782
E.coli	A10536	0.004	$\leq$0.002	0.025	0.007	0.004	0.007	0.007
E.coli	A25922	0.013	0.007	0.049	0.013	0.013	0.013	0.025
E.coli	C4052	0.007	0.004	0.025	0.007	0.007	0.007	0.013
E.cloacae	C4008	0.004	$\leq$0.002	0.013	0.004	0.004	0.004	0.007
E.cloacae	C4009	0.013	0.007	0.013	0.013	0.007	0.013	0.013
K.oxytoca	C4022	1.563	0.782	0.782	0.782	0.391	1.563	1.563
K.pneumoniae	A10031	0.007	0.004	0.025	0.007	0.004	0.007	0.007
K.pneumoniae	C4021	0.007	0.004	0.025	0.007	0.004	0.007	0.013
P.mirabilis	A25933	0.013	0.004	0.007	0.013	0.007	0.013	0.013
P.rettgeri	A9919	0.004	0.004	0.007	0.004	0.004	0.007	0.013
S.typhimurium	C4045	0.013	0.007	0.049	0.013	0.007	0.013	0.013
S.marcescens	A27117	0.013	0.007	0.025	0.013	0.007	0.013	0.013
P.aeruginosa	A10145	1.563	1.563	3.125	3.125	1.563	3.125	3.125
P.aeruginosa	C4028	0.004	$\leq$0.002	0.007	0.007	0.004	0.007	0.007
P.aeruginosa	A27853	0.782	0.782	1.563	1.563	0.782	1.563	1.563

Table 3 (Continued)

Strain		Compound of Ex.19	Compound of Ex.23	CTX	CAZ
S.pyogenes	A8668	0.007	0.013	0.007	0.098
S.pyogenes	C4003	0.007	0.013	0.007	0.196
S.aureus	A29213	0.782	0.782	0.782	6.25
S.aureus	C4036	0.782	0.782	0.782	6.25
MRSA	C1060	25	25	100	100
S.epidermidis	A12228	0.391	0.391	0.391	3.125
E.coli	A10536	0.025	0.025	0.013	0.049
E.coli	A25922	0.098	0.098	0.049	0.196
E.coli	C4052	0.049	0.025	0.013	0.098
E.cloacae	C4008	0.013	0.013	0.007	0.025
E.cloacae	C4009	0.098	0.049	0.049	0.098
K.oxytoca	C4022	50	12.5	0.782	0.782
K.pneumoniae	A10031	0.013	0.007	0.004	0.098
K.pneumoniae	C4021	0.013	0.013	0.004	0.049
P.mirabilis	A25933	0.007	0.007	0.013	0.049
P.rettgeri	A9919	0.004	0.007	0.004	0.025
S.typhimurium	C4045	0.049	0.025	0.013	0.196
S.marcescens	A27117	0.049	0.049	0.049	0.098
P.aeruginosa	A10145	25	12.5	25	3.125
P.aeruginosa	C4028	0.004	0.007	$\leq$0.002	0.013
P.aeruginosa	A27853	12.5	6.25	12.5	1.563

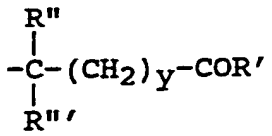
CLAIMS

1. A compound of the formula:



(I)

wherein, R_1 is hydrogen, or a lower alkyl, C_3-C_4 alkenyl, C_3-C_4 alkynyl or cycloalkylalkyl group, a fluoro-substituted lower alkyl group represented by the formula: $-(CH_2)_xF$ in which x is an integer of 1 to 3, or a carboxy-substituted alkyl group represented by the formula:



wherein R′ is a hydroxy, amino or C_1-C_4 alkoxy group; R" and R"′, which may be the same or different, represent hydrogen or a C_1-C_3 alkyl group, or R" and R"′ together with the carbon atom to which they are attached may form a C_3-C_7 carbocyclic ring; and y is an integer of 0 to 3;

R_2 and R_3, which may be the same or different, represent hydrogen, or a lower alkyl, amino, carboxy-substituted lower alkyl, hydroxy-substituted lower alkyl or C_3-C_7 cycloalkyl group;

n is an integer of 1 or 2; and

the 2-oxo-heterocyclic moiety is fused with the pyridine ring to form a 2,3- or 3,4-fused ring substituent at 3-position of the cephem nucleus; or a

pharmaceutically acceptable salt, physiologically hydrolyzable ester or solvate thereof.

2. The compound of Claim 1, wherein R_1 is a methyl, ethyl, cyclopropyl, fluoromethyl, 2-carboxyprop-2-yl or carboxymethyl group; R_2 is hydrogen, or a methyl, ethyl, cyclopropyl, amino or hydroxyethyl group; and R_3 is hydrogen or a methyl group.

3. The compound of Claim 1, which is 7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2,3-(1H,4H)-dioxo-pyrazino[5,6-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-[2,3(1H,4H)-dioxo-pyrazino[5,6-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-aminothiazol-4-yl)-2-propynyloxyiminoacetamido]-3-[2,3(1H,4H)-dioxo-pyrazino[5,6-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-cyclopropylmethoxyiminoacetamido]-3-[2,3(1H,4H)-dioxo-pyrazino[5,6-c]-pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyimino acetamido]-3-[2,3(1H,4H)-dioxo-pyrazino[5,6-c]-pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-yl)oxyiminoacetamido]-3-[2,3(1H,4H)-dioxo-pyrazino-[5,6-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[1-methyl-2,3(4H)-dioxo-pyrazino[5,6-c]-pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[1-ethyl-2,3(4H)-dioxo-pyrazino[5,6-c]-pyridimiummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[1-cyclopropyl-2,3(4H)-dioxo-pyrazino[5,6-c]-pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-yl)oxyiminoacetamido]-3-[1-methyl-2,3(4H)-dioxo-pyrazino[5,6-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-yl)oxyiminoacetamido]-3-[1-ethyl-2,3(4H)-dioxo-pyrazino[5,6-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-yl)oxyiminoacetamido]-3-[1-cyclopropyl-2,3(4H)-dioxo-pyrazino[5,6-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl]-2-methoxyiminoacetamido]-3-[4-methyl-2,3(1H)-dioxo-pyrazino[5,6-c]-pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(aminothiazol-4-yl)-2-fluoromethoxyimino-acetamido]-3-[2,3(1H,4H)-dioxo-pyrazino[5,6-c]-pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[1-methyl-2(3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[1-amino-2(3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[1-(2-hydroxyethyl)-2(3H)-oxo-imidazo[4,5-c]-pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2(1H,3H)-oxo-imidazo[4,5-b]pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-fluoromethoxyiminoacetamido]-3-[2(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

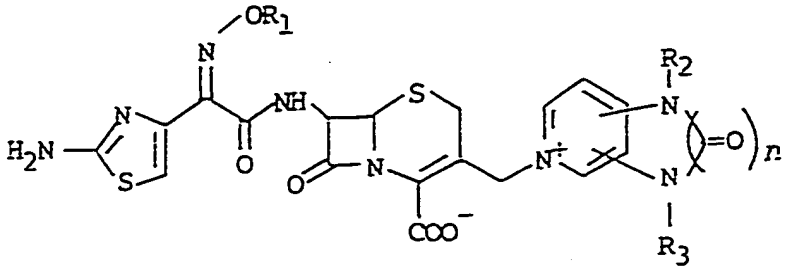
7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-fluoromethoxyiminoacetamido]-3-[1-methyl-2(3H)-oxo-imidazo[4,5-c]-pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-fluoromethoxyiminoacetamido]-3-[1-amino-2(3H)-oxo-imidazo[4,5-c]-pyridiniummethyl]-3-cephem-4-carboxylate;

7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-fluoromethoxyiminoacetamido]-3-[2(1H,3H)-oxo-imidazo[4,5-b]pyridiniummethyl]-3-cephem-4-carboxylate; or

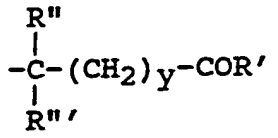
7-ß-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-[2(1H,3H)-oxo-imidazo[4,5-c]-pyridiniummethyl]-3-cephem-4-carboxylate.

4. A process for preparing a compound of the formula:



(I)

wherein R_1 is hydrogen, or a lower alkyl, C_3-C_4 alkenyl, C_3-C_4 alkynyl or cycloalkylalkyl group, a fluoro-substituted lower alkyl group represented by the formula: $-(CH_2)_xF$ in which x is an integer of 1 to 3, or a carboxy-substituted alkyl group represented by the formula:



wherein R′ is a hydroxy, amino or C_1-C_4 alkoxy group; R" and R"′, which may be the same or different, represent hydrogen or a C_1-C_3 alkyl group, or R" and R"′ together with the carbon atom to which they are attached may form a C_3-C_7 carbocyclic ring; and y is an integer of 0 to 3;

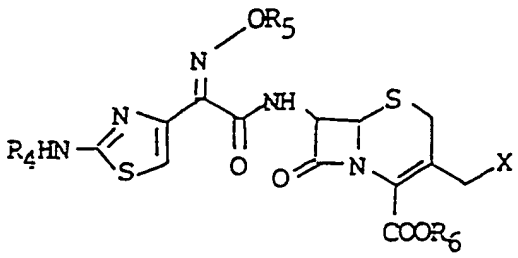
R_2 and R_3, which may be the same or different, represent hydrogen, or a lower alkyl, amino, carboxy-substituted lower alkyl, hydroxy-substituted lower alkyl or C_3-C_7 cycloalkyl group;

n is an integer of 1 or 2; and

the 2-oxo-heterocyclic moiety is fused with the pyridine ring to form a 2,3- or 3,4-fused ring substituent at 3-position of the cephem nucleus; or a

pharmaceutically acceptable salt, physiologically hydrolyzable ester or solvate thereof, which comprises the steps of:

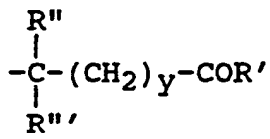
reacting a compound of the formula:



(II)

wherein R_4 is an amino protecting group;

R_5 is hydrogen or a lower alkyl, C_3-C_4 alkenyl, C_3-C_4 alkynyl or cycloalkylalkyl group, a fluoro-substituted lower alkyl group represented by the formula: $-(CH_2)xF$ in which x is an integer of 1 to 3, or a carboxy-substituted alkyl group represented by the formula:

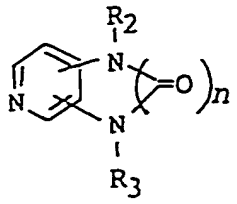


wherein R′ is a hydroxy, amino or C_1-C_4 alkoxy group; R" and R"′ may be the same or different and represent hydrogen or a C_1-C_3 alkyl group, or R" and R"′ together with the carbon atom to which they are attached may form a C_3-C_7 carbocyclic ring; and y is an integer of 0 to 3;

R_6 is a carboxyl protecting group; and

X is a leaving group;

with a compound of the formula:



(III)

wherein R_2, R_3 and n have the same meaning as defined above and the 2-oxo-heterocyclic moiety is fused with the pyridine ring to form a 2,3- or 3,4-fused ring in the presence of an organic solvent; and

then, if necessary, removing the amino protecting group and/or the carboxyl protecting group.

5. The process of Claim 4, wherein the organic solvent is selected from the group consisting of a nitrile solvent such as acetonitrile and propionitrile; an alkyl halide solvent such as chloroform, carbon tetrachloride and dichloromethane; an ether solvent such as tetrahydrofuran and dioxane; an amide solvent such as N,N-dimethylformamide; an ester solvent such as ethylacetate and methylacetate; a ketone solvent such as acetone, methyl ethyl ketone and methyl isobutyl ketone; a sulfoxide solvent such as dimethylsulfoxide; and an aromatic hydrocarbon solvent such as benzene and toluene.

6. The process of Claim 4, wherein the compound of the formula (II) is used in an amount of from 1 to 2 equivalents based on 1 equivalent of the compound of the formula (III).

7. The process of Claim 4, wherein a compound of the formula (II) in which X is an acetoxy group is first silylated with a silylating agent to protect the carboxy group at 4-position and the amino group of the substituent at 7-position, and the resulting silylated compound is then reacted with trimethyl silyliodide to form a compound of the formula (II) in which X is iodine, followed by reacting

with a silylated fused pyridine of the formula (III).

8. The process of Claim 4, wherein the silylating agent is selected from the group consisting of mono- or bis-trimethylsilylacetamide, N-methyl-N-(trimethylsilyl)acetamide, N,O-bis(trimethylsilyl)trifluoroacetamide, N-methyl-N-(trimethylsilyl)trifluoroacetamide (MSTFA), and hexamethyldisilazane (HMDS).

9. The process of Claim 4, wherein the reaction is carried out in the presence of one or more stabilizing agents.

10. The process of Claim 9, wherein the stabilizing agent is selected from the group consisting of sodium iodide, potassium iodide, sodium bromide, potassium bromide, and potassium thiocyanate.

11. A pharmaceutical composition which comprises a therapeutically effective amount of one or more of the cephalosporin compounds of the formula (I) according any of Claims 1 to 3, or a pharmaceutically acceptable salt, physiologically hydrolyzable ester or slovate thereof, in association with a pharmaceutically acceptable carrier, excipient, or other additives therefor.

12. A compound of the formula (I) according to any of Claims 1 to 3 for use as antibiotics.

13. Use of a compound of the formula (I) as defined in any of Claims 1 to 3 for manufacturing a medicament for antibiotic use.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 92/00016

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl.[5]: C 07 D 519/00, 501/46; A 61 K 31/545

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl.[5]: C 07 D 519/00, 501/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4 748 172 (A. S. KATNER) 31 May 1988 (31.05.88), see claims 1-3; column 2, line 5 to column 3, line 50; column 8, line 1 to column 9, line 36.	1-13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 July 1992 (01.07.92)	13 July 1992 (13.07.92)

Name and mailing address of the ISA/	Authorized officer
AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 VIENNA	Mazzucco e.h.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 92/00016

In Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
US A 4748172	31-05-88	AU A1 34189/84	26-04-85
		AU B2 574107	30-06-88
		CA A1 1225390	11-08-87
		DK A0 4891/84	12-10-84
		DK A 4891/84	18-04-85
		EP A2 138552	24-04-85
		EP A3 138552	19-03-86
		ES A1 536728	16-11-85
		ES A5 536728	16-12-85
		ES A1 8602816	16-03-86
		FI A0 844000	11-10-84
		FI A 844000	18-04-85
		GB A0 8425453	14-11-84
		GB A1 2148289	30-05-85
		GB A0 8627171	10-12-86
		GB A1 2181136	15-04-87
		GB B2 2148289	23-09-87
		GB B2 2181136	25-05-88
		HU A2 35687	29-07-85
		HU B 195512	30-05-88
		IL A0 73230	31-01-85
		JP A2 60105685	11-06-85
		NZ A 209833	29-04-88
		PH A 21040	03-07-87
		PT A 79357	01-11-84
		PT B 79357	20-11-86
		SU A3 1360587	15-12-87
		ZA A 8407926	28-05-86
		US A 4692443	08-09-87